

cancer is falsely called malignant. The type of the disease not so associated is called benign. The two types look alike but can, I believe, be differentiated by careful analysis.

The cancers associated with acanthosis nigricans are highly malignant, non-pigmented adenocarcinomas originating in the stomach or other abdominal organs in 92%, and in the breast, lung, etc., in 8%. Not a single patient has been cured by treatment of the cancer. The cancers occur mostly in the middle-aged but also in the very young and very old. Acanthosis nigricans may precede the cancer by many years, may start simultaneously with, or it may follow cancer. It appears, therefore, that neither acanthosis nigricans nor cancer causes the other. An activating influence of cancer on acanthosis nigricans, however, cannot be denied.

Acanthosis nigricans not associated with cancer may assume the form of a unilateral pigmented verrucous nevus. It starts at birth, in childhood or at puberty. Sex hormones seem to have a stimulating influence on this benign type of the disease. As in the case of melanoma or certain physiological pigmentations, these patients are subjected at puberty to a physiologic barrage of sex hormones which result in hyperpigmentation and other epithelial changes. Studies of the 17 keto-steroids in young and middle-aged men and women suffering from acanthosis nigricans gave normal values. The parallel action of the cancer agent and the sex hormones on the two types of the dermatosis seems noteworthy.

If an individual develops acanthosis nigricans after puberty he will sooner or later show an internal cancer and the cutaneous disease will become more intense with the manifestation of cancer. Young people, however, may have "malignant" acanthosis nigricans before puberty.

Treatment of the malignant type consists in early recognition and removal of the tumor. In the benign type the lesions sometimes regress spontaneously after puberty.

When it was found that there were no recorded familial cases of the malignant type of acanthosis nigricans, such as had been found in the benign type, an investigation of the genetics of the disease under the auspices of the American Cancer Society was undertaken. Furthermore, in this study an effort is being made to determine whether adenocarcinoma occurs in a higher percentage in the families of patients with acanthosis nigricans than in the ordinary population. Particular difficulties were encountered. In addition to all the known handicaps of genetic studies of cancer in man, one cannot be certain whether cancer victims in the older generations had also shown the cutaneous changes, possibly to a mild degree. If the individual has not yet reached puberty or cancer age, acanthosis nigricans is not likely to be noted. Are genetic carriers of

the dermatosis those with a great number of pigmented moles, and what is the "normal" amount of moles? Genetic carriers of cancer may not have been recognized because family members were not examined for any special metabolic feature on which cancer associated with acanthosis nigricans might be based. Those who transmit the disease might have exhibited such a disturbance to a lesser degree than patients with overt manifestations.

If we should succeed in establishing malignant acanthosis nigricans as a separate disease, a dermatosis might emerge which would, not in 50% but in 100% of cases, be an indicator of internal cancer and might point the way to the biology of certain malignant tumors.

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#### The Junction Nevus, Forerunner of the Malignant Melanoma and Its Differential Diagnosis from the Standpoint of the Dermatologist.

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The pigmented hairy and warty nevi have always been difficult to classify and no logical clinical classification has ever appeared feasible. Therefore, a simple anatomic basis on which to classify them has given us the best chance to simply describe these lesions and to gain definite knowledge as to which of them are potentially dangerous and which generally remain benign throughout their

entire course. We have therefore classified the pigmented hairy and warty nevi as

1. Intra-epidermal Nevi
2. Junction Nevi
3. Intradermal Nevi
4. Blue Nevi
5. Mixed types

The name "junction" was derived from the fact that the cells constituting this nevus arise at the epidermal-dermal junction. Of the group this is the only one which may give rise to a malignant melanoma or nevocarcinoma. Clinically, however, any of the above types may resemble the junction nevus so closely in clinical appearance that only on microscopic examination can one be certain of the diagnosis.

The mixed lesions are particularly confusing because they comprise combinations of any of the above types and generally this can only be recognized on microscopic examination.

Classically the junction nevus is usually small in size, not over 2-3 cm. as a rule, slightly elevated and smooth surfaced. Occasionally the surface may be soft, warty, or uneven, but it never is a hard warty lesion. The color may vary from light brown to brownish-black, or it may even be blue-black. Hairs are not present except in exceptional cases.

Junction nevi may appear at any time in life or may be present at birth. Clinically and microscopically they are indistinguishable regardless of the time of their appearance, but their behavior and prognosis is different. Those present from earliest infancy as a rule grow slowly or not at all, and if they become nevocarcinomas they metastasize more slowly and prognosis following radical treatment is successful in a relatively high percentage of cases. Those appearing in adult life, after puberty, grow more rapidly, metastasize more promptly and the outlook in these cases is always extremely grave. The percentage of cures is low in this group.

Since junction nevi, like all other nevi, are not more prone to cancer development than normal skin, most of these lesions can and should be left alone. Only when they are located at sites of extreme trauma, hands and feet, etc., is it safer to remove them prophylactically. Such removal may be accomplished with the sacrifice of a minimum of surrounding normal skin. This is ample in most cases but if early changes to nevocarcinoma are found, a wider excision may then be deemed advisable.

It should be emphasized that junction nevi are benign and that adequate removal is a perfectly safe procedure without danger of aggravating the local lesion or causing metastasis. It is because of believing that a lesion is benign, when actually it is already malignant, that trouble results from a removal predicated on this erroneous basis. Even then the error can be corrected following microscopic examination of the tissue.

The danger of malignant melanoma or nevocarcinoma can be greatly minimized by the early removal of questionable or badly located junction nevi. To advise removal of all of them is ridiculous, but it is equally bad and far more dangerous to suggest leaving them all alone. We should continually stress that the highest percentage of cures results from prophylactic removal of the earliest lesions.

There are two types of pigmented nevi most likely to be confused with the junction nevus. The first is the benign pigmented intra-epidermal nevus and the second the blue nevus. Less frequently, even the intra-dermal nevus may be confused with the junction nevus. The reason the pigmented intra-epidermal nevus is so frequently confused is because it is a smooth pigmented area devoid of hairs but often with deep black pigment and when located on the hands and feet, where thickness or elevation are difficult to make out, it is almost impossible to be certain whether the lesion is an intra-epidermal or junction nevus. The junction nevus usually shows some thickening but in certain areas this is not easily determined. This point was brought home to me recently by a patient who had about 60 small pigmented nevi on his trunk and extremities. One on the foot was removed and proved to be an intra-epidermal nevus while a similar mark on the back proved to be a junction nevus. Therefore, probably all of the others, not removed, and scattered over his body, belonged in one of these two categories and one would have had to remove each one individually to be certain of its exact type. Would it be advisable to treat indiscriminately all of these nevi with solid carbon dioxide, electrocoagulation, desiccation, etc? It is only fair to state that our rare instances of the development of malignant melanoma or nevocarcinoma following inadequate destruction of junction nevi have resulted from this practice.

The typical blue nevus, because of its blue-black color, can usually be differentiated clinically from the junction type but if the blue nevus is more brownish or brownish-black in color and rather superficially located in the cutis, confusion does frequently result. The benign pigmented intra-epidermal nevus does not terminate as nevocarcinoma or malignant melanoma but in rare instances it has terminated as a carcinoma.

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— Congenital Anomalies (Nevi) and Their Relationship to Cancer and Melanoma. *Penn. Med. Jour.*, pp. 1-8, June, 1941.

Discussion by H. Z. LUND, Western Reserve University, Cleveland, O.

From the standpoint of the surgical pathologist, recognition of early melanoblastoma and distinction from benign nevus are extremely important. The first feature which is looked for is junctional proliferation because most, if not all, melanoblastomas arise in the epidermis or at the dermo-epidermal junction. Traub and Keil have stressed this and awakened many to awareness of it. However, the emphasis has been insufficiently critical and there has been an acceptance by some dermatologists and pathologists that the presence of junctional proliferation at any age and of any degree is evidence of a potentially malignant lesion. Such a conclusion is drawn from the article by Traub and Keil. Actually the feature of junctional proliferation becomes significant if it is unusual in degree for a given age, as, for example, the finding of a nevus of a middle-aged person which has the histological characteristics of a nevus of childhood; i.e., the cells are largely junctional in distribution, resemble epithelium and there is little evidence of differentiation to ordinary nevus cells and cells associated with fibrils. Such an appearance leads to the suspicion that the lesion is incipient and growing. (The clinical evidence obtained in our own analysis of the duration of growth of such lesions was variable and conflicting, permitting no final conclusion. Additional study is needed.) The pathologist is to be guarded in excluding melanoblastoma in these cases, but until more conclusive evidence is obtained, a positive diagnosis must rest on this finding plus additional changes, including (a) excessively large, irregularly scattered or otherwise bizarre masses or nests of cells at the dermo-epidermal junction, (b) deep penetration of large cells without differentiation to small nevus cells and fibrillar forms, (c) more mitotic figures than are usual, (d) atypical and pleomorphic cells, (e) invasion, (f) trophic changes, and (g) inflammation, other than folliculitis, which is not accounted for by trauma.

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The term "junction nevus" has been criticized because such designation includes both "A" and "AB" nevi, for which it could be

legitimately used, and, in addition, the oblique premalignant (or actually malignant, depending on the criteria used) disorder called "lentigo maligna" by Dubreuilh. My preference is to designate as pigmented nevi only those lesions composed of benign melanoblastic cells (nevus cells).

Dr. Traub has again emphasized the necessity for microscopic examination of nevi and tumors with which they may be confused. He has shown with excellent colored photographs, a "junction nevus" and an "intraepidermal nevus" which cannot be distinguished clinically. On the basis of his excellent colored photomicrographic slides of the two disorders, it would seem that the first satisfies fully all the requirements of "lentigo maligna" of Dubreuilh. The second is composed entirely of epithelial cells and contains no neoplastic melanoblasts, and would seem to belong in the group of benign epidermal neoplasms (Becker, S. W.: Benign Epidermal Neoplasms, *Arch. Dermat. and Syph.*, 26:838 (Nov.) 1932) and could be called "benign epithelioma."

At any rate, it seems more scientific to classify pathologically rather than to perpetuate the older designation "nevus" in the sense of a "mark."

#### The Development of Epidermal Pigmentation in the Negro Fetus.

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Fetal Negro skin constitutes excellent material for the study of melanogenesis. Surprisingly, no systematic survey, throughout the fetal stages, had previously been made. The main advantages reside primarily in the high potentiality for melanin production of specialized cells which reveal their activity early in fetal life. They are the dendritic melanoblasts which remain distinct, both morphologically and functionally, from ordinary epithelial cells. They are the sole producers of melanin both in the epidermis and in the papillae of hair follicles. The distribution and significance of dendritic cells in the adult human skin, both white and pigmented, recently was studied by Billingham.

The derivation of mammalian melanoblasts from the neural crest has been demonstrated by Rawles (1947). In the fetal Negro